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Solvent free Synthesis of 2-[(5-methyl-1,3-benzoxazol-2-yl)sulfanyl] Acetohydrazide Derivatives as Novel Antimicrobial and Antitumor Agents

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

In pursuit of designing novel chemical entities with antitumor and antimicrobial activities, 2-[(5-methyl-1,3-benzoxazol-2-yl)sulfanyl]acetohydrazidederivatives have been synthesized as a scaffold of a series of amine derivatives, these analogs were on reductive amination with solvent free condition. All the synthesized compounds were assessed for antibacterial, antifungal, and antitumor activities against standard strains. The compounds 3a, 3b and 3g showed highest degree of inhibition against *A. flavus* and compounds 3a, 3b, 3d and 3h Showed highest degree of inhibition against *C. albicans*, compounds 3a,3e and 3g has shown the encouraging antibacterial activityresults against *E. coli* and compounds 3a, 3b and 3h exhibited a promising activity against *B. subtilis.* Compounds 3a, 3b and 3c exhibited promising antitumor activity.

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Keywords: Benzoxazole; solvent free condition; antitumor; antimicrobial.

1. INTRODUCTION

Benzoxazole skeleton have been found in numerous biological and pharmaceutical substances and which showed wide spectrum of pharmaceutical properties. In support for this study, substituted benzoxazoles showed various activities including antineoplastic, antitubercular, anthelmintic, and antimicrobial [1], anti-HIV, antifungal, antiprotozoal [2-7]. "The transformation of amines through different aldehydes is an important method in synthetic chemistry because of their benefit as intermediates for the preparation of agrochemicals and pharmaceuticals" [8-9]. It is thought worthwhile to carry out the synthesis of title compounds. In point of view to obtain some new chemical entities with together effective pharmacophores in a distinct molecular framework for the increased biological activities. The synthesis of benzoxazoles were made by many methods including Natural Sunlight Photocatalytic Synthesis [1] and solvent free methods [10].

"In account of the aforementioned information and with the extension of the former investigations on benzoxazole skeleton and its pharmacological activities" [11-17], the preparation of a new series of compounds (Fig. 6) have been achieved. The present work sheds light on the cost effective solvent free synthetic route for the synthesis of sequence of 2-[(5-methyl-1,3-benzoxazol-2-yl)sulfanyl]acetohydrazide derivatives. The synthesized derivatives have been subjected to biological activities, which displayed significant activities against all the strains.

2. METHODOLOGY

By taking the sample of compounds in a glass capillary tube beingsealed at one end, melting points weredetermined in an electrically heated apparatus,which are uncorrected. The purity and reaction progress of all the compounds were checked by TLC on silica gel plates using n-Hexane, ethyl acetate solvent system and spots located by UV and iodine chamber. All the chemicals used in this were purchased from Sigma-Aldrich and SD Fine. IR spectra were recorded using KBr pellets on a Perkin Elmer Spectrophotometer. ^{1}H-NMR spectra on Agilent400 MHz Spectrophotometer and chemical shifts were expressed as ppm and TMS as internal standard. Mass spectra were recorded on Xevo G2-XS Qtof.

2.1 Synthesis of 2-[(5-methyl-1,3-benzoxazol-2-yl)sulfanyl] Acetohydrazide (2)

Methyl-[(5-methyl-1,3-benzoxazol-2-yl)sulfanyl]acetate (1 g, 0.0039 mol, 1eq) was added to ethanol (50 mL) and hydrazine hydrate (0.22 mL, 0.0047 mol, 1.2 eq) was added slowly The reaction mixture was stirred under reflux in absolute alcohol for 4 hour. Progress of the reaction was confirmed by TLC (Chloroform: Methanol in 7:3 ratio). Reaction mixture was then poured to ice water to obtain compound 2 [18-22].

White solid; yield (90%), MP.(184-186˚C); IR (KBr, ucm-1): 1592 (C=N), 3330 (N-H); 1H NMR (400 MH, DMSO) δ: 2.4 (s, 3H), 4.02 (s, 2H), 4.32 (br, 2H, NH2), 7.07-7.48 (m, 3H), 9.4 (br, 1H, NH) (D_2O exchangeable); 13C NMR (DMSO): δ 21 (CH3), 39 (CH2), 110 – 135 (aromatic carbons), 146 (C=N), 166(C=O); MS (m/z): 237 (M+).

2.1.1 General procedure for the synthesis of 2-[(5-methyl-1,3-benzoxazol-2-yl)sulfanyl] acetohydrazide derivatives 3(a-h)

"A 2-[(5-Methyl-1,3-benzoxazol-2-yl)sulfanyl] acetohydrazide amine (1mmol) was ground with a substituted aldehyde (1 mmol) for 15 to 20 minutes in an agate mortar and pestle at room temperature (25˚C) under solvent free conditions. To the resulting mixture 1:1 ratio of Sodium borohydride and boric acid and then the mixture was added ground for 20-30 minutes until TLC showed complete disappearance of the aldehyde. The reaction mixture was washed with water and further purified by recrystallization with ethanol" [23,10,24-26].

2.1.2 General procedure for the synthesis of 2-[(5-methyl-1,3-benzoxazol-2-yl)sulfanyl] acetohydrazide derivatives 3(a-h)

A 2-[(5-Methyl-1,3-benzoxazol-2-yl)sulfanyl] acetohydrazide amine (1mmol) was ground with a substituted aldehyde (1 mmol) for 15 to 20 minutes in an agate mortar and pestle at room temperature (25˚C) under solvent free conditions.

To the resulting mixture 1:1 ratio of Sodium borohydride and boric acid and then the mixture was added ground for 20-30 minutes until TLC showed complete disappearance of the aldehyde. The reaction mixture was washed with water and further purified by recrystallization with ethanol [23,10,24-26].

2.1.3 2- [(5-methyl-1, 3-benzoxazol-2-yl)sulfanyl]-N'-(thiophen-2-ylmethyl)acetohydrazi-de (3a)

Grey colour solid, yield (75 %) MP (Melting Point) (235-236˚C);IR(cm-1): 1166 (C-N bond streching):1H NMR (400 MH, DMSO) δ : 2.33 (s,3H), 4.22 (s,1H), 4.6 (s, 2H), 7.04 (s, 2H), 7.30 - 7.64 (Aromatic-H's),11.80 (s, 1H);13C NMR (DMSO) δ : 21.3 (CH3), 34.1 (CH2), 35.00 (CH2), 110-150 (Aromatic carbons), MS (m/z): 333 (M+)

2.1.4 N'-(furan-2-ylmethyl)-2-[(5-methyl-1,3-benzoxazol-2-yl)sulfanyl]acetohydrazide (3b)

Grey colour solid, yield (73 %), MP (250-253˚C); IR(cm-1): 1156 (C-N str.):1H NMR (400 MH, DMSO) δ: 2.33 (s,3H), 4.22 (s,1H), 4.6 (s, 2H), 7.04 (s, 2H), 7.30 - 7.64 (Aromatic-H's),11.80 (s, 1H);13C NMR (DMSO) δ : 21.3 (CH3), 34.1 (CH2), 35.00 (CH2), 110-150 (Aromatic carbons) MS (m/z): 317 (M+)

2.1.5 2-[(5-methyl-1,3-benzoxazol-2-yl)sulfanyl]-N'-(2-nitrobenzyl)acetohydrazide (3c)

Grey colour solid, yield (75 %), MP (296-298˚C);; IR(cm-1): 1156 (C-N bond streching):1H NMR (400 MH, DMSO) δ: 2.41 (s,3H), 3.98 (s,1H), 4.6 (s, 2H), 7.04 (s, 2H), 7.30 - 7.64 (Aromatic H's),11.66 (s, 1H);13C NMR (DMSO) δ : 21.42 (CH3), 34.01 (CH2), 35.00 (CH2), 109-150 (Aromatic carbons) ; MS (m/z): 372 (M+)

2.1.6 N'-(4-chlorobenzyl)-2-[(5-methyl-1,3-benzoxazol-2-yl)sulfanyl]acetohydrazide (3d)

Grey colour solid, yield (74 %), MP (280-282˚C); IR(cm-1): 1152 (C-N bond stretching)1H NMR (400 MH, DMSO) δ: 2.45 (s,3H), 3.97 (s,1H), 4.62 (s, 2H), 7.02 (s, 2H), 7.30 - 7.64 (Aromatic-H's),11.66 (s, 1H);13C NMR (DMSO) δ : 21.42 (CH3), 29.01 (CH2), 34.00 (CH2), 109-147 (Aromatic carbons), 183.72 (C=O); MS (m/z): 362 (M+).

2.1.7 N'-benzyl-2-[(5-methyl-1,3-benzoxazol-2-yl)sulfanyl]acetohydrazide (3e)

Grey colour solid, yield (77 %), MP (230-232˚C); IR(cm-1): 1142 (C-N bond stretching):1H NMR (400 MH, DMSO) δ: 2.41 (s,3H), 3.97 (s,1H), 4.64 (s, 2H), 7.01 (s, 2H), 7.11 - 7.71(Aromatic-H's),11.07 (s, 1H);13C NMR (DMSO) δ : 21.55 (CH3), 34.17 (CH2), 34.57 (CH2), 109-150 (Aromatic carbons), 169.37 (C=O); MS (m/z): 327 (M+).

2.1.8 N'-(2-chlorobenzyl)-2-[(5-methyl-1,3-benzoxazol-2-yl)sulfanyl]acetohydrazide (3f)

Grey colour solid, yield (78 %), MP (285-287˚C) ; IR(cm-1): 1164 (C-N bond stretching):1H NMR (400 MH, DMSO) δ: 2.39 (s,3H), 4.25 (s,1H), 4.68 (s, 2H), 7.10 (s, 2H), 7.11 - 7.71 (Aromatic-H's),11.92 (s, 1H);13C NMR (DMSO) δ : 21.38 (CH3), 34.98 (CH2), 35.17 (CH2), 110-164 (Aromatic carbons), 168.69 (C=O); MS (m/z): 361 (M+).

2.1.9 N'-(2-bromobenzyl)-2-[(5-methyl-1,3-benzoxazol-2-yl)sulfanyl]acetohydrazide (3g)

Light brown colour solid, yield (80%), MP (298-299˚C); IR(cm-1): 1144 (C-N bond stretching):1H NMR (400 MH, DMSO) δ: 2.45 (s,3H), 3.92 (s,1H), 4.61 (s, 2H), 6.98 (s, 2H), 7.12 – 8.0 (Aromatic-H's), 11.18 (s, 1H);13C NMR (DMSO) δ : 21.39 (CH3), 34.16 (CH2), 34.27 (CH2), 110-164 (Aromatic carbons), 169 (C=O); MS (m/z): 406 (M+).

2.1.10 2-[(5-methyl-1,3-benzoxazol-2-yl)sulfanyl]-N'-(4-nitrobenzyl)acetohydrazide (3h)

Grey colour solid, yield (71 %), MP (280-281˚C); IR(cm-1): 1174 (C-N bond stretching):1H NMR (400 MH, DMSO) δ: 2.31 (s,3H), 4.12 (s,1H), 4.68 (s, 2H), 6.74 (s, 2H), 7.08 – 8.0 (Aromatic-H's), 12.02 (s, 1H);13C NMR (DMSO) δ : 21.37 (CH3), 34.90 (CH2), 39.36 (CH2), 110-164 (Aromatic carbons), 168 (C=O); MS (m/z): 372 (M+).

2.2 Biological Activities

2.2.1 Antibacterial activity

"The newly synthesized 2-[(5-methyl-1,3-benzoxazol-2-yl)sulfanyl] acetohydrazide derivatives were tested for antibacterial activity against bacterial strains, *Escherichia coli* (ATTC-8739), *Bacillus subtilis* (ATTC-6633) by agar well diffusion method" [27-28]. The 24 hr old Mueller-Hinton broth culture of test bacteria were swabbed on sterile Mueller-Hint on agar plates using sterile cotton swab followed by punching wells of 6 mm with the help of sterile cork borer. The standard drug (Streptomycin 1mg/mL of sterile distilled water), compounds 3(a-h) (25mg/mL of 10% DMSO), and control (10% DMSO) were added to the respectively label dwells. The plates were allowed to stand for 30 minutes and were incubated at 37°C for 24 hr in upright position and the zone of inhibition was recorded and tabulated in Table 2. And compounds 3a,3e and 3g have shown the very good activity against *E.coli* and compounds 3a, 3b and 3h showed considerable activity against *B. subtilis.*

2.2.2 Antifungal activity

"The Compounds3(a-h)were screened for anti-fungal activity against fungal A. flavus and C. albicans strain with fluconazole as a standard drug respectively. The compounds 3a, 3b and 3g Showed inhibition against *A. flavus* when compared with the standard drug fluconazole. Compounds 3a, 3b, 3d and 3h showed inhibition against C. albicans when compared with the standard drug fluconazole" [29-30].

2.2.3 Antitumor activity

"The antitumor activity against HepG2, human liver cancer cell lines were estimated using the 3-[4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assay, Cells were dispensed in a 96-well sterile microplate (5 × 104 cells/well) and incubated at 37°C with series of different concentrations in DMSO, of 3(a-h) compounds for 48 h in a serum-free medium prior to the MTT assay. After incubation, media were carefully removed, and 40 µL of MTT (2.5 mg/mL) was added to each well and then incubated for an additional 4 h. The purple formazan dye crystals were solubilised by the addition of 200 µL of DMSO. The absorbance was measured at 570 nm using multi-Mode micro plate reader analysed using Megalen software. The relative cell viability was expressed as the mean percentage of viable cells compared to the untreated control cells. All experiments were conducted in triplicate and repeated in three different days. All the values were represented as mean ± SD and IC50s were determined" [31-34].

Table 1. Antibacterial activity

Compounds	**Bacteria**			
	E. coli		***B. subtilis***	
	25 mg/mL	**50 mg/mL**	**25 mg/mL**	**50 mg/mL**
2	1.5±0.6	1.9±0.8	1.4±0.3	1.6±0.5
3a	1.8±0.1	2.1±0.30	1.9±0.24	2.4±0.29
3b	1.5±0.2	1.8±0.5	2.0±0.12	2.4±0.12
3c	1.4±0.12	1.7±0.6	1.3±0.21	1.8±0.6
3d	1.6±0.2	2.1±0.4	1.5±0.12	2.2±0.24
3e	1.7±0.23	2.2±0.5	1.6±0.2	2.1±0.21
3f	1.4±0.22	1.8±0.21	1.3±0.21	2.1±0.32
3g	1.8±0.25	2.2±0.20	1.6±0.31	2.2±0.31
3h	1.5±0.12	1.9±0.21	1.6±0.23	2.3±0.21
Streptomycin	1.8±0.25	2.6±0.28	2.1±0.32	2.5±0.34

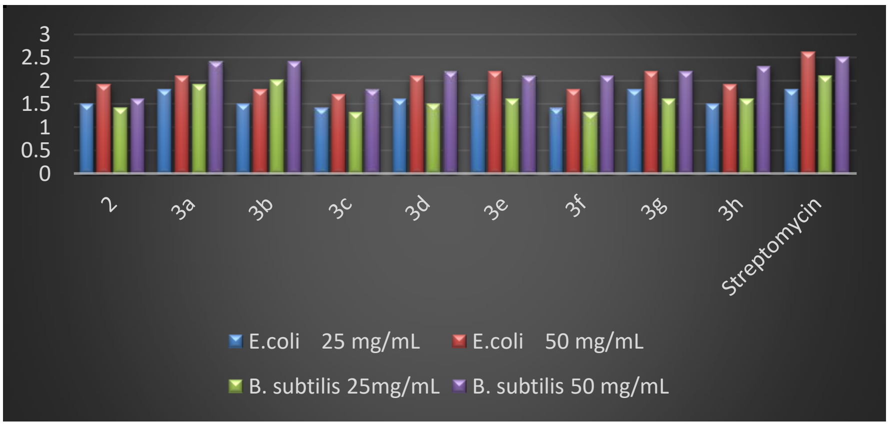


Fig. 1. Antibacterial activity of Compounds 2 &3(a-h)

Table 2. Antifungal activity

Compounds	Fungi			
	A. flavus		*C. albicans*	
	25 mg/mL	50 mg/mL	25 mg/mL	50 mg/mL
2	25	53	36	46
3a	44	74	38	78
3b	44	70	55	64
3c	24	69	35	71
3d	36	72	38	73
3e	37	69	39	71
3f	25	67	29	65
3g	38	70	37	69
3h	41	71	38	75
Fluconazole	38	77	39	81

***Values are represented as the mean ± SEM.**
Values are significant for the standard at 0.005 level of significance.

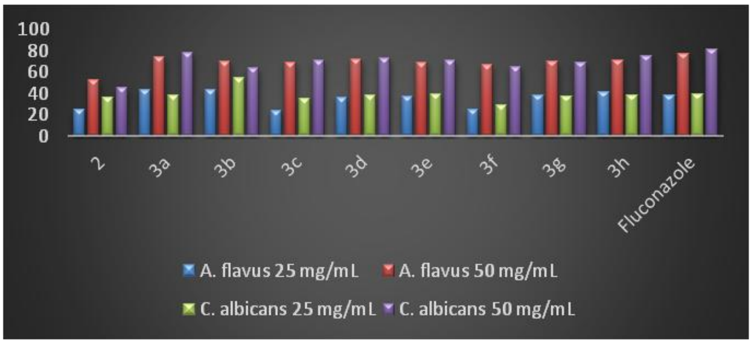


Fig. 2. Antifungal activity of Compounds 2 &3(a-h)

Table 3. Antitumor activity

Compounds	% of inhibition 25 mg/ml	% of inhibition 50 mg/ml	% of inhibition 100 mg/ml	IC 50 Value
2	31.4 %	52.2 %	59.4%	96
3a	32. 6 %	56.4 %	62.8 %	109
3b	30. 4 %	56.9 %	63.4 %	110
3c	34. 4 %	60.1 %	67.3 %	112
3d	30.6 %	56.2%	64.2 %	106
3e	30.4 %	54.4 %	60.1 %	104
3f	29. 6%	48.1 %	52.3 %	97
3g	30. 4%	48.3 %	52.4 %	98
3h	30. 6%	50.1 %	60.3 %	104
Std			76.4 %	136

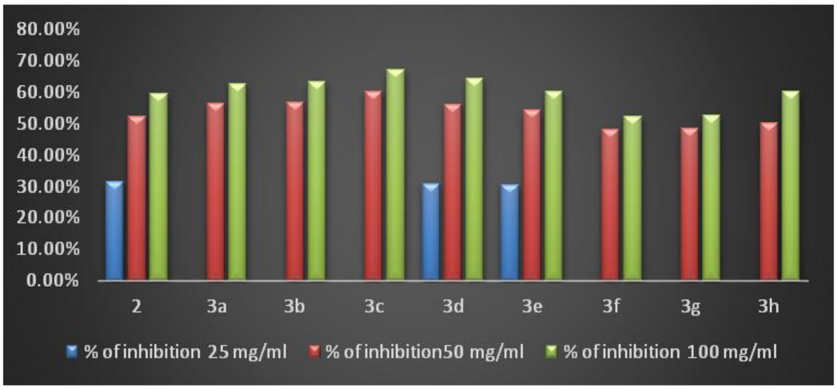


Fig. 3. Antitumor activity of Compounds 2 &3(a-h)

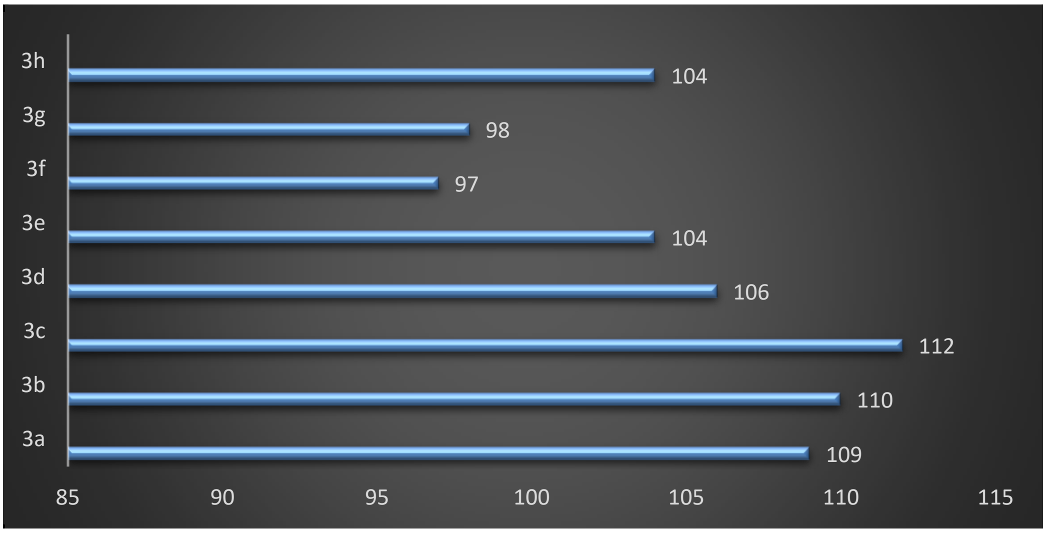
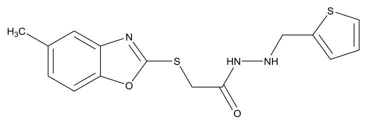
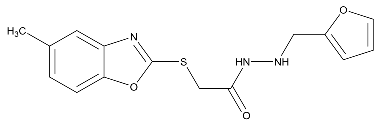
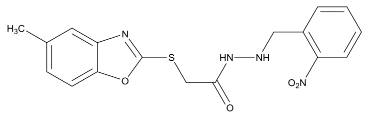
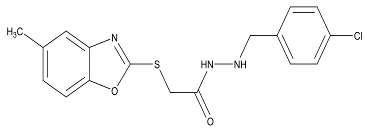
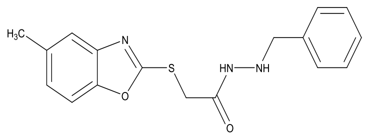
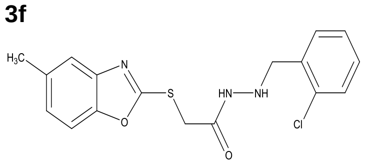
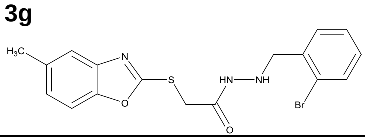
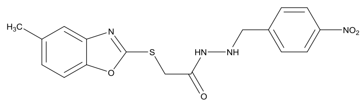


Fig. 4. IC 50 valueof Compounds 2 &3(a-h)

Table 4. Physical data of compounds 3(a-h)

Compound	Molecular formula	Molecular weight	M.P (°C)
3a 	$C_{15}H_{15}N_3O_2S_2$	333.42	235-236
3b 	$C_{15}H_{15}N_3O_3S$	317.36	250-253
3c 	$C_{17}H_{16}N_4O_4S$	372.40	296-298
3d 	$C_{17}H_{16}ClN_3O_2S$	361.84	280-282
3e 	$C_{17}H_{17}N_3O_2S$	327.40	230-232
3f 	$C_{17}H_{16}ClN_3O_2S$	361.84	285-287

Compound	Molecular formula	Molecular weight	M.P (°C)
3g 	$C_{17}H_{16}BrN_3O_2S$	406.30	298-299
3h 	$C_{17}H_{16}N_4O_4S$	372.40	280-281

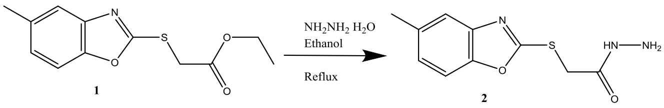


Fig. 5. Synthetic route for the synthesis of Compound 2

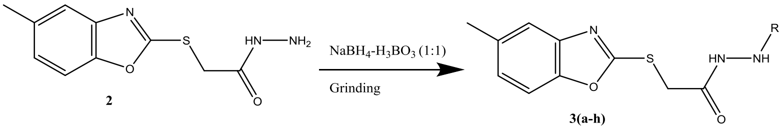


Fig. 6. Synthetic route for the synthesis of Compounds 3(a-h)

3. RESULTS AND DISCUSSION

3.1 Chemistry

2-[(5-Methyl-1,3-benzoxazol-2-yl)sulfanyl] acetohydrazide derivatives were prepared from solvent free reductive amination reaction with different aldehydes. The compound Methyl-[(5-methyl-1,3-benzoxazol-2-yl) sulfanyl] acetate 1 was used to prepare [9], further the target molecules 2(a-h) were synthesized using the intermediate 2-[(5-methyl-1,3-benzoxazol-2-yl)sulfanyl] acetohydrazide 2. The compound 1 was treated with hydrazine hydrate (0.22 mL, 0.0047 mol, 1.2 eq). The reaction mixture was stirred under reflux in absolute alcohol for 4 hour. Progress of the reaction was confirmed by TLC (Chloroform: Methanol in 7:3 ratio). Reaction mixture was then poured to ice water to obtain compound 2.

The compounds 2(a-h) were prepared by treating 2-[(5-methyl-1,3-benzoxazol-2-yl)sulfanyl] acetohydrazide amine (1mmol) with different substituted aldehydes (1 mmol) for 15 to 20 minutes in an agate mortar and pestle at room temperature (25˚C) under solvent free conditions. To the resulting mixture was added 1:1 ratio of Sodium borohydride and boric acid was added and then the mixture was ground for 20-30 minutes until TLC showed complete disappearance of the aldehyde. The reaction mixture was washed with water and further purified by recrystallization.

In the ^1H NMR of 2a, the disappearance of -NH2 proton and appearance of -NH supported the formation of product. The mass peak of compounds 3a showed at M+ 333 and for compound 3b M+ 317 which matches their molecular weights. The construction of compounds 3(c-h) followed a similar method of preparation.

The compounds 3(a-h) were screened for antimicrobial and antitumor activities. The compounds 3a, 3b and 3g Showed highest degree of inhibition against A. flavus and compounds 3a, 3b, 3d and 3h Showed highest degree of inhibition against C. albicans, compounds 3a,3e and 3g has shown the very good antibacterial activity against E. coli and compounds 3a, 3b and 3h shows remarkable activity against *B. subtilis*. Compounds 3a, 3b and 3c exhibitedpotential antitumor activity.

4. CONCLUSION

The overall study reports the synthesis of different compounds via solvent free methods in good yield. This method is functionally simple and is specially free form the use of toxic metals, solvents and other oxidants. The target molecules were characterized and confirmed by mass, IR, ^{1}HNMR and ^{13}CNMR analysis and screened for antitumor and antimicrobial activities. Theexpected target compounds were prepared, structurally confirmed by IR, ^{1}H NMR, ^{13}C NMRand mass spectral analysis and *in-vitro* screenedfor their biological activities. The data describedhere in indicates that compound 3a, 3b and 3ghas developed as potentially active compounds.These molecules have shown significant outcomesas compared to standard drug and considered aspotential molecules for further study.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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